Application No. 09/519,246

Stuart K. Williams et al.

For: Endovascular Graft Coatings

Filed: March 6, 2000

APPENDIX C

Affidavit of Dr. Patrick Guire

OMB No. 0925-0226
Expiration Date 12/90

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

SMALL BUSINESS INNOVATION RESEARCH PROGRAM

PHASE II GRANT APPLICATION

LEAVE BLANK		
TYPE	ACTIVITY	NUMBER 0789HLBI.DLC
REVIEW GROUP		FORMERLY
COUNCIL/BOARD *(Month/year)*		DATE RECEIVED

1a. TITLE OF APPLICATION *(Do not exceed 56 typewriter spaces)*
In Vivo Testing of an Improved Vascular Prosthesis

1b. Phase I Grant No.
1 R43 HL40280-01

2. PRINCIPAL INVESTIGATOR ☐ New Investigator

2a. NAME *(Last, first, middle)*

2b. SOCIAL SECURITY NO.

2c. POSITION TITLE
Manager of Biological Research

2d. MAILING ADDRESS *(Street, city, state, zip code)*
Bio-Metric Systems, Inc.
9924 West Seventy-Fourth Street
Eden Prairie, MN 55344

2e. TELEPHONE *(Area code, number and extension)*
(612) 829-2700

3. HUMAN SUBJECTS
☒ NO ☐ YES ☐ Exemption # _____ OR ☐ Form HHS 596 enclosed

4. VERTEBRATE ANIMALS
☐ NO ☒ YES Assurance #3759-01

5. SMALL BUSINESS CERTIFICATION
☒ Small Business
☐ Minority and disadvantaged
☐ Woman-owned

6. INVENTIONS
☒ NO ☐ YES ☐ Previously reported OR ☐ Not previously reported

7. DATES OF ENTIRE PROPOSED PHASE II PERIOD	8. COSTS REQUESTED FOR FIRST 12-MONTH BUDGET PERIOD		9. COSTS REQUESTED FOR ENTIRE PROPOSED PHASE II PERIOD	
	8a. Direct Costs	8b. Total Costs	9a. Direct Costs	9b. Total Costs
FROM: July 1, 1990 THROGH: June 30, 1992	$	$	$	

10. PERFORMANCE SITES *(Organizations and addresses)*
Bio-Metric Systems, Inc.
9924 West Seventy-Fourth Street
Eden Prairie, MN 55344

Cardiovascular Surgery Research Laboratories
University of Minnesota
Minneapolis, MN 55455

11. APPLICANT ORGANIZATION *(Name, address and congressional district)*
Bio-Metric Systems, Inc.
9924 West Seventy-Fourth Street
Eden Prairie, MN 55344

3rd District, Minnesota

12. ENTITY IDENTIFICATION NUMBER
41-1356149

13. NOTICE OF PROPRIETARY INFORMATION
The information identified by asterisks (*) on pages 11-15, 20-39, 41-42, 44, 47, 51-54 of this application constitutes trade secrets or information that is commercial or financial and confidential or privileged. It is furnished to the Government in confidence with the understanding that such information shall be used or disclosed only for evaluation of this application; provided that if a grant is awarded as a result of or in connection with the submission of this application, the Government shall have the right to use or disclose the information herein to the extent provided by law. This restriction does not limit the Government's right to use the information if it is obtained without restriction from another source.

14. DISCLOSURE PERMISSION OR STATEMENT
If this application does not result in an award, is the Government permitted to disclose the title only of your proposed project, and the name, address and telephone number of the corporate official of your firm, to organizations that may be interested in contacting you for further information or possible investment?
☒ YES ☐ NO

15. CORPORATE OFFICIAL
(Name, title, address and telephone number)
Patrick E. Guire, Ph.D., V.P./R&D
Bio-Metric Systems, Inc.
9924 West 74th Street
Eden Prairie, MN 55344 (612)829-2700

16. PRINCIPAL INVESTIGATOR ASSURANCE:
I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application. Willful provision of false information is a criminal offense *(U.S. Code, Title 18, Section 1001).*

SIGNATURE OF PERSON NAMED IN 2a.
(In ink. "Per" signature not acceptable)

DATE
12/14/89

17. CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true and complete to the best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as the result of this application. A willfully false certification is a criminal offense *(U.S. Code, Title 18, Section 1001).*

SIGNATURE OF PERSON NAMED IN 15
(In ink. "Per" signature not acceptable)
Patrick E. Guire

DATE
14 Dec '89

ABSTRACT OF RESEARCH PLAN

NAME, ADDRESS AND TELEPHONE NUMBER OF APPLICANT ORGANIZATION

Bio-Metric Systems, Inc.
9924 West 74th Street
Eden Prairie, MN 55344
(612) 829-2700

YEAR FIRM FOUNDED	NO. OF EMPLOYEES (*Include all affiliates*)
1979	46

TITLE OF APPLICATION

In Vivo Testing of an Improved Vascular Prosthesis

KEY PROFESSIONAL PERSONNEL ENGAGED ON PROJECT

NAME	POSITION TITLE	ORGANIZATION
	Manager of Biological Research	Bio-Metric Systems
	Associate Biochemist	Bio-Metric Systems
	Senior Biomedical Engineer	Medtronic Promion
	Dir. of Card. Surgery	University of Minnesota
, Ph.D.	Prof. Path., Macr. Sci and Biomed. Engineering	Case Western Reserve University

ABSTRACT OF RESEARCH PLAN: State the application's long-term objectives and specific aims, making reference to the health-relatedness of the project, describe concisely the methodology for achieving these goals, and discuss the potential of the research for technological innovation and commercial application. Avoid summaries of past accomplishments and the use of the first person.

The abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application. Since abstracts of funded applications may be published by the Federal Government, do not include proprietary information. DO NOT EXCEED 200 WORDS.

No adequate small diameter vascular prostheses are now commercially available, with the major reasons for loss of patency being thrombus formation and neointimal fibrous hyperplasia. This project is designed to improve prosthesis function by covalently immobilizing cell adhesion proteins onto the prosthesis lumen. The proteins are expected to improve initial endothelial cell (EC) attachment, subsequent EC growth, and ultimately promote the establishment of a stable and non-hyperplastic neointima. Phase I results showed that proprietary BSI photoimmobilization technology covalently immobilized active fibronectin and type IV collagen onto four vascular prosthesis materials, with the coated materials showing greatly improved attachment and growth of EC's. Phase II proposes to: 1) optimize protein coatings (as evaluated by promotion of EC cell attachment and growth *in vitro)* and then 2) evaluate coated prostheses *in vivo* for improved patency when implanted intrafemorally in dogs. The dog implants will be conducted with and without autologous seeded endothelial cells. Also, antithrombic agents (heparin and hirudin) will be immobilized along with the cell adhesion proteins and evaluated for effectiveness at inhibiting thrombus formation and improving the *in vivo* development of a stable endothelial layer. Small diameter prostheses with greatly improved patency rates would be used for both coronary and peripheral artery reconstructions.

Provide key words (8 maximum) to identify the research or technology.

Vascular Graft, Vascular Prosthesis, Biomaterial, Biocompatible

Provide a brief summary of the potential commercial applications of the research.

The technology developments proposed here should greatly improve the long-term patency of small diameter vascular prosthesis, and expand the use of artificial prostheses in peripheral and coronary reconstruction.

TABLE OF CONTENTS

Number pages consecutively at the bottom throughout the application. Do not use suffixes such as 5a, 5b. Type the name of the Principal Investigator at the top of each printed page and each continuation page.

SECTION 3. APPENDIX *(Three sets) (No page numbering necessary for Appendix)*

Number of publications and manuscripts accepted for publication (Not to exceed 10): 1 (Appendix 5)
Other items *(list):*

Appendix 1. Fetal Bovine Cornea Explant Assay
Appendix 2. Scanning Electron Microscopic Examination of Vascular Prostheses Before and After Exposure to Solvents
Appendix 3. Cell Outgrowth from Cornea Explants onto TFE-PET Prostheses
Appendix 4. Cell Outgrowth from Cornea Explants onto Porous SR Prostheses
Appendix 5. Reprint of Hirudin Paper Presented at the Cardiovascular Science and Technology Meeting, Louisville, KY, Dec. 1989.

☐ Form HHS 596 if Item 3, page 1, is checked "YES" and no exemptions are designated.

RESEARCH PLAN

A. Specific Aims

The objective of this proposed Phase II research program is to develop an improved small diameter vascular prosthesis that will demonstrate significantly better long-term patency than any currently available prosthesis. The project is based on two hypotheses: 1) a vascular prosthesis whose lumen is lined with a stable and non-hyperplastic layer of endothelial cells will demonstrate superior long-term patency, and 2) an appropriate luminal coating of cell adhesion proteins (possibly with an added antithrombic agent) will promote the attachment and growth of endothelial cells to produce a stable and non-hyperplastic neo-intima.

Four porous vascular prosthesis materials will be coated and evaluated during this project: expanded polytetrafluoroethylene (ePTFE, ref. 1), porous silicone rubber (SR, ref. 2), woven polyethylene terephthalate plasma coated with tetrafluoroethylene (TFE-PET, ref. 3), and porous polyurethane (PU, ref.4). BSI's proprietary photoimmobilization technology will be used to covalently immobilize cell adhesion proteins and peptides (with and without antithrombic agents) onto each prosthesis material. The coated prosthesis materials will be evaluated *in vitro* for promotion of endothelial cell attachment and growth and for antithrombic activity. Then coated prostheses will be implanted into dogs (with and without being seeded with endothelial cells) and evaluated for endothelial cell growth, thrombus formation, intimal hyperplasia, and patency.

Phase I and other previous BSI results (5-8) show that: 1) cell adhesion proteins and peptides are efficiently immobilized onto implant polymers by this photochemistry, and 2) the immobilized cell adhesion proteins/peptides improve *in vitro* endothelial cell attachment and growth on several polymers. Immobilization of antithrombic agents (such as heparin or hirudin) in addition to the cell adhesion proteins/peptides may improve thromboresistance during the time that endothelial cells are growing to confluence on the prosthesis.

The specific objectives of this Phase II research are to:

1. Immobilize cell adhesion proteins (fibronectin, laminin, and type IV collagen), peptides (that contain the cell attachment activities of these proteins), and antithrombic agents (e.g., heparin and hirudin) onto each polymer material.
2. Conduct *in vitro* assays to:
   a. Optimize the levels of immobilized proteins or peptides required to maximize attachment and growth of isolated vascular endothelial cells (both canine and bovine).
   b. Optimize the activity of each antithrombic agent.
3. Implant coated and uncoated prostheses in dogs (with and without being seeded with autologous dog vascular endothelial cells) to evaluate endothelial cell growth, thrombus formation, intimal hyperplasia, and patency.
4. Conduct *in vivo* toxicity studies to evaluate the prosthesis coatings.

The coatings developed in this project can be readily adapted to current manufacturing processes and should greatly improve endothelialization and long-term patency of small diameter vascular prostheses.

B. Significance

Currently available small diameter vascular prostheses ($\leq$4 mm) are inadequate [9], with failure usually resulting from thrombus formation (short-term failure) or neointimal fibrous hyperplasia (long-term failure) [10]. Until recently, the usual approach to improving the biocompatibility of vascular implants and other implant devices was to use materials that react as little as possible with surrounding tissues [9,11]. However, there is an increasing recognition that no implant materials are truly inert. This has led to the development of materials and surface modifications that promote tissue interaction to produce a stable tissue-implant interface [6,9,11]. Clearly, the nature of the interfacing biomaterial surface governs the processes which are involved in biological responses to materials. If this interaction results in overgrowth of the implanted material by one or more layers of cells but is not accompanied by thrombus formation, hyperplasia or inflammation, the resulting tissue-coated material would be tissue compatible [6,9,12,13], and would also resist bacterial growth [14,15]. For small diameter vascular prostheses, it would be especially useful to

promote the adhesion and growth of vascular endothelial cells to line the luminal surface, thus producing superior blood compatibility.

One approach to promoting endothelial cell attachment and growth on prostheses would be to immobilize cell adhesion proteins derived from the extracellular matrix that are known to promote these processes. Cell adhesion is a multi-step process consisting of an initial attachment (characterized by weak binding and little cell shape change) followed by stronger adhesion and cell spreading [review by ref. 16]. The initial attachment can be mediated by non-specific binding between cells and a protein-free substrate, whereas adhesion and spreading generally require specific ligand-receptor interactions between the cell and proteins on the substratum surface [16,17].

Proteins known to mediate cell adhesion *in vitro* and *in vivo* include collagen, fibronectin and laminin [17-19]. Of the several types of collagen that have been identified, type IV is most often reported to promote cell adhesion [19,20]. Fibronectin and type IV collagen are each reported to mediate the adhesion of numerous cell types (including endothelial cells), whereas laminin is reported to be more specific for epithelial cells [17-20]. Also, type IV collagen has been isolated from the human aorta and localized in the subendothelium [21]. Therefore, fibronectin and type IV collagen would seem to be good choices for promoting the attachment and growth of endothelial cells on vascular prostheses.

An immediate concern in using these proteins is that factors that promote cell adhesion might also promote platelet aggregation and thrombosis. Although this is true for types I and III collagen, current evidence indicates that type IV collagen is not thrombogenic either in solution or in its *in vivo* conformation [21A]. Both fibronectin and type IV collagen are reported to induce some platelet attachment, but neither promotes platelet activation nor aggregation [21A]. Therefore, both proteins should be non-thrombogenic and suitable for use with vascular protheses.

Endothelial cell seeding procedures often use adsorbed fibronectin to promote the adhesion of isolated endothelial cells to the luminal surface of small diameter vascular grafts (e.g., several studies in ref. 9). Although these procedures have resulted in some endothelialization and improved patency in dogs, baboons, and apparently even man [22], most of the cells are lost upon exposure to blood flow [23]. An improvement on this approach might be to covalently immobilize the proteins. BSI had a recent SBIR Phase I project which immobilized cell adhesion proteins onto polystyrene microcarriers to improve cell attachment in agitated bioreactors [24]. Results from this project (shown in Figure 1) demonstrate that gelatin covalently bound to the polystyrene beads (COV GEL) produced greater attachment and retention of each cell type (Vero and CHO cells) in an agitated medium than did gelatin that was adsorbed (ADS GEL). Similarly, we would expect covalently immobilized cell adhesion proteins to improve the attachment and retention of endothelial cells on vascular prostheses exposed to blood flow; thus increasing the probability of producing complete and stable endothelialization of the prosthesis lumen. Complete endothelialization would have the dual benefits of producing both a non-thrombic surface and inhibiting smooth muscle invasion of the pseudointima [10].

Utilizing native cell adhesion proteins to modify implant device surfaces would present two potential problems: 1) these proteins are quite large and lose biological activity upon being denatured; therefore special handling and storage procedures would be required for a commercially marketed prosthesis coated with these proteins; and 2) FN and IV COL are derived from human blood and tissue, respectively, and would require verification that they are free of human viruses. Fortunately, the cell adhesion and growth promoting activities of these proteins reside in specific, localized regions that are rapidly being identified, sequenced, and synthesized. The first two such regions to be reported were the peptide sequences RGD in fibronectin [26] and YIGSR in laminin [27]. Each cell adhesion peptide has been synthesized, immobilized, and reported to stimulate attachment of specific cell types with similar biological activity as the native protein [26,27]. Recently, additional regions of FN and LM and a region specific to IV COL have been reported to stimulate adhesion and growth by other cell types [28-31]. Such peptides would provide stable and inexpensive substitutes for the intact proteins, and could be immobilized onto polymers to avoid both the need for special storage requirements and problems associated with proteins derived from human tissues.

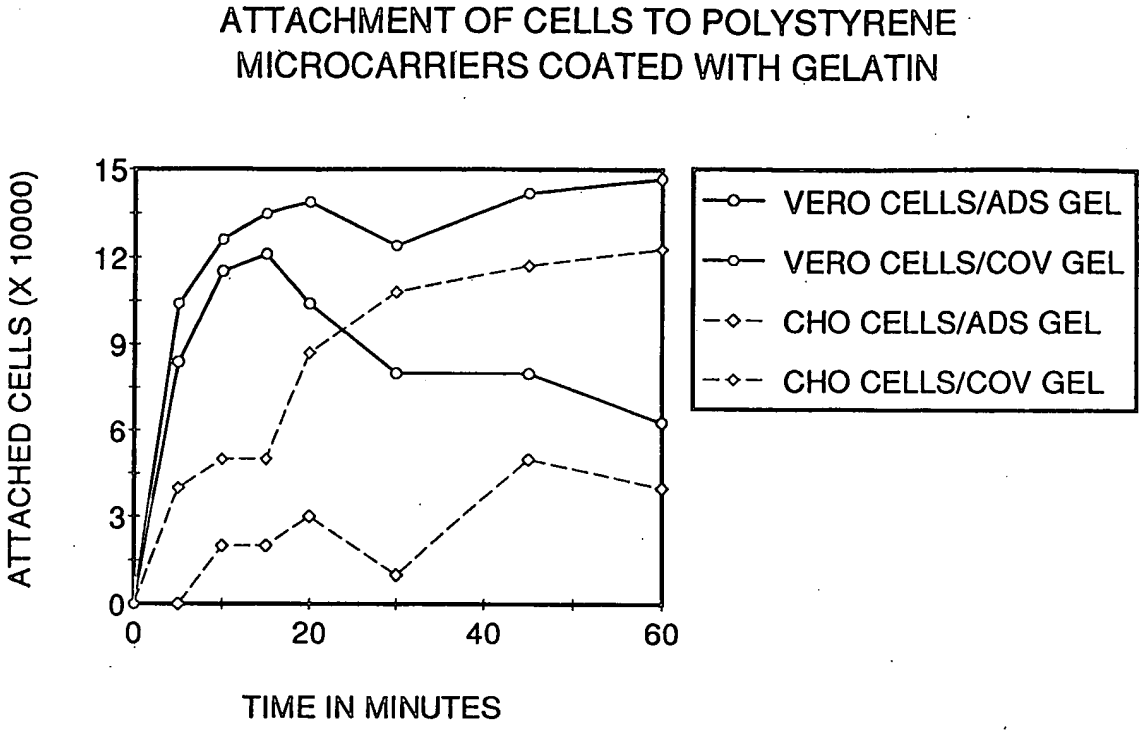

Figure 1. Cell attachment to immobilized gelatin in a stirred bioreactor.

BSI has just completed a SBIR Phase I project to develop procedures for immobilizing cell adhesion peptides onto cell culture surfaces [32]. Three peptides derived from FN (RGD FN peptide) and LM (F-9 and D-12 LM peptides) were compared to intact FN, LM, and IV COL for promotion of endothelial cell attachment and growth (Figure 2). All three peptides promoted endothelial cell attachment comparable to intact FN and LM, but four-fold less than IV COL (Fig. 2A); however the peptides produces subsequent growth of endothelial cells that was greater than IV COL (Figure 2B). We anticipate that ongoing research to identify attachment peptides in IV COL will lead to peptides that promote endothelial cell attachment comparable to intact IV COL [e.g., ref. 31]. Procedures developed in the peptide Phase I project will be utilized in this proposed Phase II project to immobilize onto prosthesis polymers specific cell adhesion peptides that promote the adhesion and growth of vascular endothelial cells.

Although cell adhesion proteins promote the attachment and growth of cells on polymer surfaces, the rate of colonization and selectivity for endothelial cells might be increased by the use of growth factors. Such a use of growth factors to promote endothelial cell ingrowth from surrounding tissue was recently proposed by Sharefkin et al [25]. Endothelial cell growth factor and other growth factors are reported to stimulate the growth of vascular endothelial cells [33]. However, growth factors are very expensive to purchase and unstable upon storage; therefore, they do not appear to be good candidates for a commercial vascular prosthesis. No experiments using immobilized growth factors are planned in Phase II.

The goal of this project is to achieve biocompatibility by promoting the attachment and growth of endothelial cells. As was indicated in the "Specific Aims" section, vascular prostheses will be coated with cell adhesion proteins or peptides and implanted with and without being seeded with homologous vascular endothelial cells. Once the endothelial cells have grown to confluence, the surface should be nonthrombogenic. However, unseeded prostheses and areas not totally covered with seeded cells may not be completely compatible with blood during the time prior to complete cell overgrowth. When placed in contact with blood, areas not covered with cells will be subject to adsorption of serum proteins which then provide attachment sites for the subsequent adhesion of platelets and leukocytes [35,36]. In an attempt to minimize this potential problem, antithrombic agents will be immobilized along with the cell adhesion proteins and peptides.

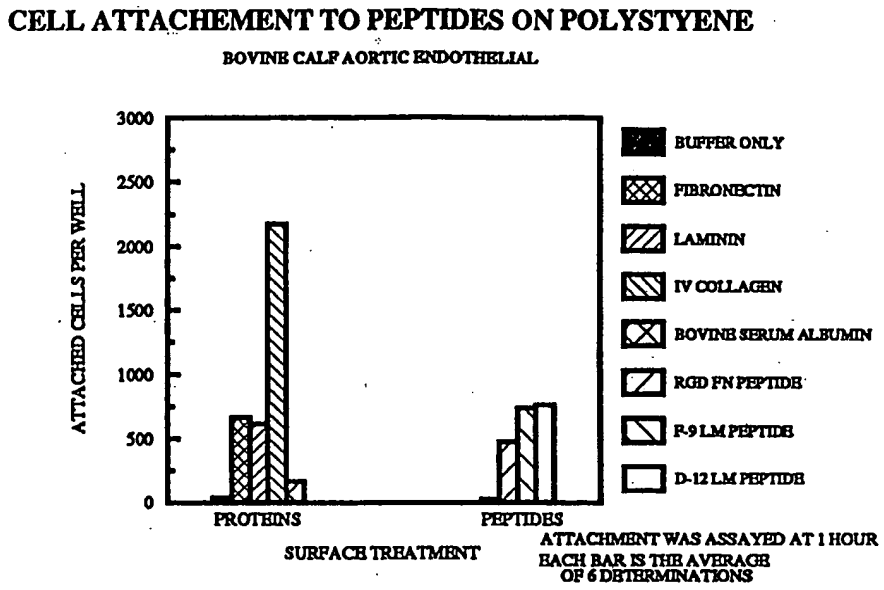

Figure 2A. Endothelial cell attachment to polystyrene coated with cell adhesion proteins and peptides.

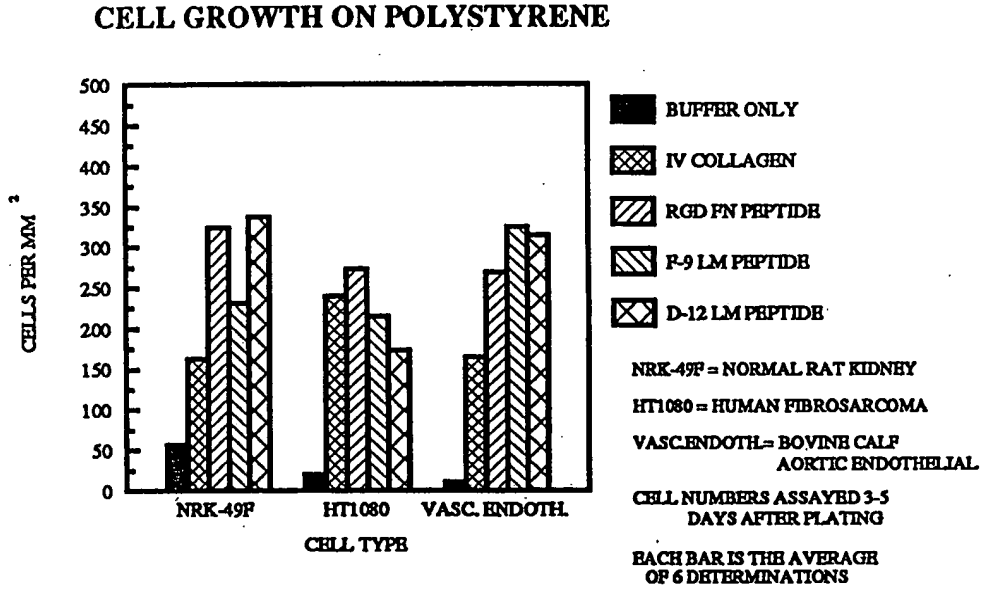

Figure 2B. Cell growth on polystyrene coated with cell adhesion proteins and peptides.

Of the various classes of antithrombic agents, four types act at cell surface receptors and might be effective if immobilized onto polymer surfaces. These are heparin, hirudin, prostacyclin, and the fibrinolytic enzymes, streptokinase and urokinase [35-38]. Two of these agents (heparin and hirudin) will be evaluated in this project; we believe these two agents are most likely to both be effective when immobilized and be compatible with subsequent cell overgrowth. Immobilized heparin has been reported to retain its anticoagulating activity [39,40] and to also inhibit thrombus formation in *in vitro* [35], and *in vivo* systems [41]. It has the additional property of inhibiting smooth muscle proliferation without inhibiting endothelial cells [42]. Some heparin preparations have been reported to induce platelet aggregation [36,43]. This undesirable action of heparin can be minimized by using low molecular weight fractions of heparin (MW 1,500 to 8,000 daltons), which are reported to retain *in vitro* antithrombic activity while producing

considerably less aggregation of platelets than does unfractionated heparin (MW 3,000 to 40,000 daltons) [43,44]. BSI is currently developing procedures to immobilize heparin using our photochemistry [44A]. Also, in a recently completed SBIR Phase I project, BSI has developed procedures to immobilize hirudin, the leech anticoagulant protein [45]. The immobilized hirudin binds thrombin with a stoichiometry of about one thrombin per two hirudin, and almost completely inhibits the proteolytic activity of the thrombin [45].

The photochemistry used to covalently immobilize biomolecules during this project has not previously been used for medical devices implanted into humans. Therefore, their potential toxicity is a significant concern. BSI has recently had reagent samples evaluated for toxicity by independent testing laboratories. The reagent tested consisted of benzoylbenzoyl polyethylene glycol (BBA-PEG). BBA is the photogroup used in Phase I and proposed for the Phase II study. PEG is a polymer well-known for its biocompatability and was coupled to the BBA by chemistry similar to that used to couple BBA to the biomolecules used in this project. The BBA-PEG was evaluated after being photoactivated, so that potential toxicity of both photoactivated and any residual unreacted photogroups would be evaluated. An Ames Salmonella/mammalian microsome mutagenicity test was performed by North American Science Associates, Inc. (Northwood, OH). The test evaluated 1 gm of BBA-PEG suspended in 10 ml of 10% saline (which is a several thousand fold higher concentration than would be associated with implanted materials), and results showed neither inhibition of growth nor mutagenic changes in *Salmonella typhimurium.* The other test evaluated photoactivated BBA-PEG for growth inhibition and cytotoxicity of Chinese hamster ovary (CHO) cells and was conducted by SRI International (Menlo Park, CA). Their report to BSI stated that "No effects were observed on cell growth and cloning efficiency after treatment of the cells with the test material (0.01 to 3 μg/well) with and without rat liver S9, and protein synthesis values for the treated cultures at the highest concentration were within 79% of the control values." S-9 is an Aroclor 1254-induced rat liver homogenate preparation used to metabolically activate the sample, and 3 μg of BBA-PEG per well is estimated to be 30 times the photogroup concentration that would be associated with an implant device. These results show no evidence of toxicity by photoactivated BBA.

In an additional toxicity assay, PEG, human serum albumin (HSA), and hyaluronic acid (HA) were photoimmobilized onto polysulfone dialysis fibers, implanted subcutaneously into mice, and evaluated by a pathologist after 8 and 15 days [45A]. The histopathology evaluations showed no evidence of toxicity when evaluated for the size of fibrous encapsulation, the number of macrophages present, and presence of hemorrhage or necrosis. All of the coated materials were at least as biocompatible as uncoated materials, with slightly reduced fibrous capsules being observed around the samples coated with PEG and HA. These two sets of toxicity assays showed no evidence of toxicity when BBA was coupled to PEG or was used to photoimmobilize PEG, HSA, or HA; therefore it seems unlikely that the photochemistry will demonstrate toxicity when used to immobilize other biomolecules.

The literature summarized in this section supports our hypothesis that extracellular matrix proteins (with or without antithrombic agents) immobilized on vascular prostheses will promote attachment and stable overgrowth of endothelial cells. Once cell overgrowth occurs, the prosthesis should show long-term blood compatibility and improved patency.

C. Relevant Experience

The Principal Investigator, Dr. (Manager of Biological Research), has fifteen years of graduate and postgraduate experience in the fields of cell biology, biochemistry, and biomaterial surface modification. He also has earlier experience (from 1967-1969) as a surgery technician in heart research laboratories where he conducted or assisted in several open-chest operations on dogs each week for nearly two years (see "Biographical Sketch"). He has fifteen publications in refereed journals in the area of receptor-mediated cell activation, with emphasis on calcium regulation in cultured rat gonadotrope cells [46] and sea urchin eggs [47-49]. In the latter system, he discovered two previously unknown "second messengers" that release calcium from intracellular stores [48-49].

Since joining BSI in late 1986, he has: 1) continued research into calcium regulation (by synthesizing specialty IP_3 reagents); and 2) utilized BSI's proprietary photoimmobilization technology to modify

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

NOTICE OF GRANT AWARD

DATE ISSUED: 09/26/90

GRANT NUMBER: SSS-8 (B)
2 R44 HL40280-02

TYPE OF AWARD: SMALL BUSINESS INNOVATION RESEARCH PROG
AUTHORIZED BY: 42 USC 241 42 CFR PART 52 15 USC 638

TOTAL PROJECT PERIOD:
From 09/30/90 Through 09/29/92

AWARDED BY:
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Title of Project or Area of Training
IN VIVO TESTING OF AN IMPROVED VASCULAR PROSTHESIS

Grantee Organization
BIO-METRIC SYSTEMS, INC
9924 WEST 74TH STREET
EDEN PRAIRIE, MN 55344

Principal Investigator/Program Director/Awardee
PHD
BIO-METRIC SYSTEMS, INC
9924 WEST 74TH STREET
EDEN PRAIRIE, MN 55344
03

APPROVED BUDGET
FOR BUDGET PERIOD 09/30/90 Through 09/29/91

Salaries and Wages	$
Fringe Benefits	
Total Personnel Costs	$
Consultant Costs	
Equipment	
Supplies	
Travel - Domestic	
- Foreign	
Patient Care - Inpatient	
- Outpatient	
Alterations and Renovations	
Consortium/Contractual Costs	
Other	
Trainee Stipends	
Trainee Tuition and Fees	
Trainee Travel	
TOTAL DIRECT COSTS →	$ 0

When PHS Prior Approval is required for rebudgeting, submit requests to Grants Management Official below.

AWARD COMPUTATION

DIRECT COSTS	$
INDIRECT COSTS	$*
TOTAL	$
Less Unobligated Balance [Prior Period(s)]	$ 0
AMOUNT OF THIS AWARD →	$

Base Dollars × Rate Percentage = Indirect Costs $*
0

SUPPORT RECOMMENDED FOR REMAINDER OF PROJECT PERIOD**

Budget Period	Total Direct Costs (Includes Stipends)	Stipends
03		
04	NONE	

**Subject to availability of funds and satisfactory progress.

REMARKS
AMOUNT AWARDED IS THE MAXIMUM ALLOWABLE CEILING TO BE REIMBURSED UNDER THIS GRANT.

SEE PAGE TWO

TERMS OF ACCEPTANCE: By acceptance of funds awarded under this grant, the grantee acknowledges that it will comply with terms and conditions in the following: (1) Legislation cited above; (2) Regulations cited above; (3) Special provisions noted above under remarks or attached to this notice; (4) 45 CFR Part 74 or 92, as applicable; (5) PHS Grants Administration Manual; (6) PHS Grants Policy Statement. The above order of precedence shall prevail.

FY—Common Accounting Number	CRS/Entity Identification No.	PHS List No./Object Class Code	Document Number
0-8424277	1411356149A1	/41.4B	(08)R3HL40280B

PROGRAM OFFICIAL
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DIRECTOR
DIV OF HEART & VASCULAR DISEASES
NAT. HEART, LUNG, & BLOOD INST.

PHS Grants Management Official
JEANETTE HINDE, CHIEF
GRANTS OPERATIONS BRANCH
DIVISION OF EXTRAMURAL AFFAIRS
NAT. HEART, LUNG, & BLOOD INST.

PHS 1533 Rev. 7/88 900919 0920

Copies distributed to Principal Investigator, Program Director or Awardee, and Business Office

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